REMARKS

Favorable reconsideration of this application in view of the remarks to follow and allowance of the claims of the present application are respectfully requested.

Claims 13, 14, 18, 19 and 20-31 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over the disclosures of Kuhl et al., Cancer Chemotherap. Pharmacol., 33(1), pp. 10-16 (abstract, "Kuhl et al.") in combination with Miura et al., Gan To Kagaku Ryoho 25(9), pp. 1262-5(English abstract, "Miura et al.") and Gorbunova, Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver (English abstract, "Gorbunova").

The Examiner states that Miura et al. teach the treatment of liver tumors or hepatocellular carcinomas via hepatic artery administration of doxorubicin (DX) and Lipiodol (iodized oil) to decrease tumor volume or cause remission, and Kuhl et al. teach that MMDX, as a DX analog, not only has the same tumor specificity as DX, but it is activated in the liver to a metabolite whose potency is 10 times greater. The Examiner further asserts that the nexus between the above-mentioned two references and the present invention is bridged by Gorbunova et al., which allegedly teaches that intrahepatic arterial infusion creates high concentrations of an antitumor agent in the organ affected. The Examiner therefore concludes that a person of ordinary skill in the art would have been motivated to use MMDX in hepatic artery administration with a reasonable expectation of success.

Applicants respectfully submit that the Examiner fails to establish a *prima facie* case of obviousness as discussed below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the cited reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the reference, not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully point out that the Examiner's statement that Miura et al. teach the treatment of liver tumors or hepatocellular carcinomas via hepatic artery administration of doxorubicin (DX) and Lipiodol (iodized oil) is in error. Miura et al. disclose the treatment of patients with hepatocellular carcinoma with hepatic administration of Epirubicin (EPI, not DX, EPI is an epimer of DX) in combination with Mitomycin C and Lipiodol, and EPI in combination with Mitomycin C and 5-FU.

First, the cited references, solely or in combination, do not teach or remotely suggest the claimed invention. Kuhl et al. do not teach either the use of MMDX for the treatment of solid tumors, such as liver tumor, or any "*in vivo*" activity of MMDX. According to the full-text article of Kuhl et al. (enclosed), the data reported by Kuhl et al. were all obtained using a panel of 14 human leukemia and lymphoma cell lines, not animals. In other words, Kuhl et al. only report the "*in vitro*" activity of MMDX against blood tumors. Miura et al. does not teach the treatment of liver tumors or hepatocellular carcinomas via the use of MMDX. Instead, Miura et al. disclose the treatment of patients with hepatocellular carcinoma with hepatic administration of EPI in combination with Mitomycin C and Lipiodol, and EPI in combination Mitomycin C and 5-FU. Lipiodol is the trademark name of an iodinated oily X-ray contrast medium composed of 40% iodine in poppy-seed oil, which has no anti-tumor efficacy. In other words, Miura et al. only teach the beneficial effect of a multiple therapy comprising a double

combination and a triple combination wherein EPI is only one of the components of said therapy. There is no teaching or suggestion in Miura et al. that either DX or EPI alone is beneficial to decrease liver tumor volume or cause remission. Gorbunova generally discloses that intrahepatic arterial infusion creates high concentrations of an anti-tumor agent in the organ affected, however, it does not teach or remotely suggest intrahepatic administration of MMDX. Thus, the cited references disclose the *in vitro* activity of MMDX against non-solid tumors (Kuhl et al.); a combination therapy wherein EPI is only one of the components (Miura et al.); and high concentrations of an anti-tumor agent in the organ via intrahepatic arterial infusion (Gorbunova). In view of the above disclosure, the cited references, solely or in combination, do not teach or remotely suggest the use of MMDX for the treatment of a liver cancer, particularly the intrahepatic administration of MMDX for use in the liver tumor therapy.

Second, in view of the cited references and the common knowledge in the art, one ordinarily skilled in the art would not have had any reasonable expectation of success for using MMDX in the treatment of liver tumors.

In view of the disclosure of Kuhl et al, i.e. the "*in vitro*" activity of MMDX against blood tumors, one ordinarily skilled in the art would not have reasonable expectation of success for using MMDX in the treatment of liver tumors. As discussed above, Kuhl et al. only disclose the "*in vitro*" activity of MMDX against blood tumors. It is common knowledge in the art that the *in vitro* data only support the "potency" of a drug, not its "efficacy" in animals, therefore one ordinarily skilled in the art would not be able to readily ascertain the efficacy of MMDX in the treatment of liver tumors in animals in view of the reported "*in vitro*" data. Further, solid tumors are remarkably different from blood tumors. For example, solid tumor is characteristically described as an abnormal mass of tissue that usually does not contain cysts or

liquid areas. Blood tumors, such as leukemia, generally do not form such an abnormal mass of tissue. Since blood tumors are fast growing and more responsive to chemotherapy, the corresponding chemotherapies for blood tumors and solid tumors differ considerably. In fact, it is well known in the art that many agents used in the treatment of blood tumors, such as leukemia and lymphoma, have no therapeutic efficacy against solid tumors. (See the last paragraph of the left column and the first paragraph of the first column on page 290 of Cancer, Principle & Practice of Oncology, 6th Edition, V.T. DeVita et al., enclosed.) In addition, it is common knowledge in the art that cancer chemotherapy is tumor-specific and the results of chemotherapy depend on tumor growth characteristics and on the tumor's individual resistance to the drug. (See the third paragraph of the left column on page 290 of Cancer, Principle & Practice of Oncology, 6th Edition, V.T. DeVita et al., enclosed.) This is evidenced by the "cocktail therapy" and the "lack of one drug for all" treatment in cancer chemotherapy. (See pages 291-292 of Cancer, Principle & Practice of Oncology, 6th Edition, V.T. DeVita et al., enclosed.) Hence, one ordinarily skilled in the art, knowing the considerable differences between solid tumor and blood tumor, and the tumor-specific characteristic in cancer chemotherapy, would not be movitvated to treat liver tumors with MMDX with the reasonable expectation of success in view of the "*in vitro*" activity of MMDX against blood tumors (Kuhl et al.).

In view of the disclosure of Miura et al., i.e. the beneficial effect of a multiple therapy wherein EPI is one of the components, one ordinarily skilled in the art would not have had a reasonable expectation of success for using MMDX in the treatment of liver tumors. As discussed above, there is no teaching or suggestion in Miura et al. that either DX or EPI alone is beneficial to decrease liver tumor volume or cause remission. Further, it is known in the art that

MMDX exerts its cytotoxic effect through a mode of action different from that of classical antrhracyclines like DX and EPI (See the References cited under Item 1, namely Capranico et al., Molecular Pharmacology, 45(5), 908-15, 1994, copy enclosed; Mariani et al., Invest New Drugs, 12(2), 93-7, 1994, Abstract, copy enclosed; Wassermann et al., Mol Pharmacol. 38(1), 38-45, 1990, copy enclosed; Van der Graaf et al., Cancer Chemother. Pharmacol., 35, 345-48, 1995, copy enclosed; Duran et al., Cancer Chemother. Pharmacol., 38, 210-216, 1996, copy enclosed; and Bielack et al., Anticancer Res., 15(4), 1279-84, 1995, copy enclosed;). Without the teaching of the present invention in hand, one ordinarily skilled in the art, knowing that the functional mechanisms of MMDX and EPI are different, would not be able to predict the activity of MMDX against a liver tumor based on the data of a combination therapy containing EPI.

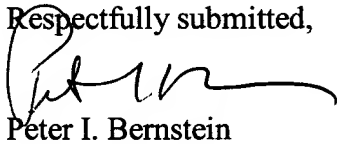
Further, there is no suggestion or motivation, either in the cited references or in the knowledge generally available to one of ordinary skill in the art, to modify the references to make and use the claimed invention. Not only do the cited references fail to teach or remotely suggest the claimed invention, but in fact, there are clinical studies stating that DX and EPI administered alone or in combination with different anticancer agents have poor efficacy in treating liver cancer (See the References cited under Item 2, namely Lai et al., Cancer, 62(3), 479-83, 1988, Abstract (enclosed); Shepherd et al., Reg Cancer Treat., 3(4), 197-201, 1990, Abstract (enclosed); Colleoni et al., Ann Oncol., 5(Suppl 8), 1994, Meeting Abstract (enclosed); Lai et al., Arch Surg., 133(2), 183-8, 1998 (enclosed); Ono et al., Semin Oncol., 24(2 Suppl 6), S6-18-S6-25, 1997, Abstract (enclosed)). In other words, the cited references teach away from the present invention that contemplates intrahepatic use of MMDX for treatment of liver cancer. One ordinarily skilled in the art, having knowledge of the above teachings, would not have been motivated to use MMDX to obtain a beneficial effect in the hepatic cancer indication.

In view of the above, applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness and the claims of the present application are not rendered obvious by the references cited in the present Office Action.

The rejections under 35 U.S.C. § 103 have been obviated; therefore reconsideration and withdrawal thereof is respectfully requested.

Thus, in view of the foregoing remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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